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(54) Title: NEUROLOGIC AGENTS FOR NASAL ADMINISTRATION TO THE BRAIN

(57) Abstract

Disclosed is a method for transporting neurologic therapeutic and/or diagnostic neurologic agents to the brain by means of the olfactory neural pathway and a pharmaceutical composition useful in the treatment and diagnosis of brain disorders.

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NEUROLOGIC AGENTS FOR NASAL ADMINISTRATION
TO THE BRAIN

Field of the Invention

The present invention is directed to a method for delivering therapeutic and/or diagnostic neurologic agents to the brain by means of the olfactory neural pathway and a pharmaceutical composition useful in the treatment and diagnosis of brain disorders.

Background of the Invention

Alzheimer's disease is an age-associated neurodegenerative disorder of the brain. The disorder is characterized histopathologically by the formation and accumulation of neurofibrillary tangles (NFT) and neuritic plaques in the brain. In particular, pathological changes associated with the disease extensively affect neurons in the olfactory bulb and its connected brain structures. Degeneration with loss of neurons has been observed in the hippocampal formation, amygdaloid nuclei, nucleus basalis of Meynert, locus ceruleus, and the brainstem raphe nuclei, all of which project to the olfactory bulb. These degenerative changes result in the loss of memory and cognitive function. In addition, there is a major loss of cortical and hippocampal choline acetyltransferase activity and degeneration of basal forebrain cholinergic neurons. The loss of odor detection in Alzheimer's patients has been attributed to necrosis of olfactory epithelium, olfactory bulbs and tracts and the prepyriform cortex.

Neurofibrillary tangles (NFT) are believed to result from the abnormal deposition of protein within the neuron structure. Research into the composition and structure of these tangles in isolated NFT-bearing neurons and in partially purified NFT preparations using a monoclonal antibody, A2B5, suggests that the Alzheimer's neurofibrillary tangles have a glycolipid antigenic marker associated with them. See C. R. Emory, et al., *Neurology* 37: 768 (1987), and C. R. Emory, et al., *Fed. Proceedings* 45: 1728 (1986). Previous studies have demonstrated that

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A2B5 reacts with polysialated gangliosides such as G_{Q1c}.
See, N. Kasai and R. K. Yu, Brain Research 277:   155
(1983).   Evidence further suggests that the molecular
substructures or epitopes characteristic of and specific
5   for Alzheimer's disease, termed "tangletopes" herein, are
other glycolipids, sulfolipids, phospholipids, and/or
phosphoproteins.   It is hypothesized that a structure of
the tangletope may involve phosphate and/or sulfate
moieties.
10   At present, there is no treatment for Alzheimer's
disease which effectively prevents or retards the
progressive neurodegeneration of the brain and the loss of
smell and cognitive decline associated with the illness.
There is also no definitive method for establishing the
15   diagnosis of Alzheimer's disease antemortem. Neurotrophic
and neuritogenic factors, such as nerve growth factor
(NGF) and gangliosides, have demonstrated therapeutic
effects in animal models and cell cultures which indicate
these substances may be of benefit to patients afflicted
20   with Alzheimer's disease.   See Frey, W.H., II and T.A.
Ala, Progress in Clinical Neuroscience 1:287-303 (1988).
Neurotrophic and neuritogenic factors are agents
that affect the survival and differentiation of neurons in
the peripheral and central nervous systems. These growth
25   promoting factors are signaling substances that are
synthesized in tissues in response to neurons capable of
responding to the factor. They bind to receptors on the
surface of nerve cells to promote neuron survival and in
some cases are incorporated into nerve cell membranes.
30   Studies further indicate that nerve growth factor (NGF),
a class of polypeptide signaling substances, may be
capable of improving cholinergic functioning which would
prevent injury-induced degeneration of basal forebrain
cholinergic neurons and improve cognitive functioning.
35   Nerve growth factor (NGF) is known to bind to receptors on
axon terminals, and can be internalized and retrogradely
transported to the cell body of neurons. See M. Seiler,

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<u>Brain Res.</u> 300:33-39 (1984). Other naturally-occurring
nerve growth promoting factors include gangliosides,
phosphatidylserine (PS), brain-derived neurotrophic
factor, fibroblast growth factors, insulin, insulin-like
growth factors, ciliary neurotrophic factor, neurotropin
3, and glia-derived nexin, and other growth factors which
are capable of acting within the brain.

Testing the effectiveness of potentially
therapeutic agents against brain disease in animal
toxicity studies and human trials has been hindered,
however, by the inability of existing procedures to
readily deliver adequate levels of the agent to affected
areas of the brain over an extended period of time.

Some experimental therapeutic agents used in the
treatment of Alzheimer's disease, such as GM-1
ganglioside, can be administered to the brain through the
bloodstream because of their ability to traverse the
blood-brain barrier. However, it is not clear that
effective levels of the ganglioside reach the affected
areas of the brain.

Other potentially therapeutic agents, such as
nerve growth factor (NGF), are unable to cross the blood-
brain barrier and must be administered to the brain by
other means. One such method of delivery is by an
intracerebroventricular pump. Use of such a pump,
however, necessitates invasive surgery which can entail a
variety of medically-related complications. Furthermore,
administration of medication by pump does not facilitate
selective delivery of medication solely to those areas of
the brain affected by disease. Consequently, healthy
areas of the brain may be adversely affected by the
neurologic agent while some diseased areas may not receive
a high enough level for adequate treatment or testing of
a drug.

An effective method of therapeutic intervention
is needed to prevent and effectively treat brain diseases
such as Alzheimer's disease, Parkinson's disease, brain

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tumors, AIDS, nerve damage from cerebrovascular disorders such as stroke, and ordinary aging. Testing the potential of various neurologic agents is an important aspect of developing treatments for neurodegenerative diseases. Since existing methods of testing possible therapeutic agents and treating brain disorders are of limited benefit, a goal of the present invention is to develop a procedure to effectively deliver neurologic agents to the brain. A particular goal of the invention is to develop a method of delivering neurologic substances to the brain to augment the level of activity against brain diseases by naturally-occurring substances. A further goal is to develop a means of selective delivery of a neurologic agent only to areas of the brain which are damaged by a brain disorder. Still another objective is to develop a composition that can cause absorption of the neurologic agent into olfactory neurons and along the olfactory neural pathway to damaged neurons in the brain. Another goal is to provide prophylactic treatment of neurodegenerative diseases and to treat and/or prevent associated loss of smell. Still another goal is to provide a method for the delivery of neurologic diagnostic reagents to the brain in order to improve the diagnosis and evaluation of patients with neurodegenerative diseases and other brain disorders.

Summary of the Invention

These and other goals are met by the present invention which is directed to a method to convey therapeutic and/or diagnostic substances to the brain for the treatment and/or diagnosis of neurologic or psychiatric disorders and a pharmaceutical composition capable of delivering a neurologic agent to the brain for use in such a method of treatment and/or diagnosis. More specifically, the method involves intranasal administration of a neurologic agent which may be absorbed into the olfactory system of the brain for the treatment

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and/or diagnosis of brain diseases and disorders such as
Alzheimer's disease, Parkinson's disease, brain tumors,
AIDS, schizophrenia, affective disorders such as
depression and mania, anxiety disorders, dependency on
addicting substances, nerve damage from cerebrovascular
disorders such as stroke, and brain changes associated
with aging. The method also involves administration of a
neurologic agent which may be a receptor-active agent, for
example, an opiate receptor antagonist, for use in
evaluating the existence and/or level of dependence on
addicting substances, for example, cocaine, heroin, and
marihuana, or for the treatment of such addictions.

According to the method of the invention, a
neurologic substance is administered to the nasal cavity
of a patient affected with Alzheimer's disease or other
disease afflicting the brain. The neurologic factor may
be applied alone or in combination with other substances.
Particular formulations may include the neurologic
substance in combination with a pharmaceutically-
acceptable carrier and/or components that may facilitate
the transfer of the neurologic agent through the nasal
mucosa and/or along the olfactory neural pathway to
damaged nerve cells of the brain.

The neurologic agent may be administered
intranasally as a powder, spray, gel, ointment, infusion,
injection, or drops. Alternatively, the neurologic agent
may be administered as eye drops.

The method of the invention may employ
transneuronal anterograde and retrograde transport of the
neurologic agent entering through the olfactory system of
the brain. Once the agent is dispensed into the nasal
cavity, the agent may transport through the nasal mucosa
by means of the peripheral olfactory neurons into the
olfactory bulb and interconnected areas of the brain such
as the hippocampal formation, amygdaloid nuclei, nucleus
basalis of Meynert, locus ceruleus, and the brainstem
raphe nuclei. The agent alone may facilitate this

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movement into the brain. Alternatively, the carrier
and/or other transfer-promoting factors may assist in the
transport of the neurologic agent into and along the
olfactory neural pathway.

5   Lipophilic substances in the form of micelles or
liposomes (lipid vesicles) may be added to the
pharmaceutical composition to enhance absorption of the
neurologic agent across the olfactory epithelium. To
augment such absorption, the neurologic agent may be
10   contained within or bound to the surface of the micelles
or liposomes. Among those substances that are preferred
additives are gangliosides such as GM-1, and phospholipids
such as phosphatidylserine (PS), which may be combined
with the neurologic agent either alone or in combination.
15   Substances that are preferred liposome additives are those
which provide vesicles bounded by one or more lipid
bilayers and are readily soluble in fats, and have an
internal cavity filled with a solvent such as water.
Suitable liposome additives include those which provide
20   unilamellar, multilamellar or paucilamellar lipid
vesicles. Unilamellar vesicles are preferred.

          Odorants may also be added to the pharmaceutical
composition to provide an odoriferous sensation and/or to
aid in inhalation of the composition. Preferably, the
25   odorant agent has an affinity for binding to odorant
binding protein (OBP) which may assist in transport of the
neurologic agent to olfactory receptor neurons. It is
also preferred that the odorant agent has an affinity for
associating with lipophilic substances, for examples,
30   liposomes and micelles added to the composition.
Preferred odorants include, for example, terpenoids such
as cetralva and citronellol, aldehydes such as amyl
cinnamaldehyde and hexyl cinnamaldehyde, esters such as
octyl isovalerate, jasmines such as ClS-jasmine and
35   jasmal, and musk 89.

          The invention further provides a method for
preventing neurodegenerative disorders. Intranasal

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administration of nerve growth promoting factors to peripheral nerve cells of the olfactory system, a purported entryway for causative agents of brain diseases, helps protect against disease in these nerve cells and
5   regenerate injured nerve cells thereby forestalling the subsequent spread of disease to susceptible areas of the brain. Although a part of the central nervous system, the neurons of the olfactory epithelium have the unusual ability to proliferate throughout adult life.   See
10   Graziadei, P.P.C. and Monti Graziadei, G.A., J. Neurocytol. 8:1-18 (1979).

The invention is also directed to a pharmaceutical composition which may be used in the method of medical treatment and/or prophylaxis. The composition
15   is comprised of a neurologic agent in combination with a pharmaceutical carrier and/or the foregoing optional additives which promote the transfer of the agent within the olfactory system.

The neurologic agent is the active ingredient of
20   the composition. For treatment and/or prophylaxis, it is preferred that the neurologic agent promote nerve cell growth and survival or augment the activity of functioning brain cells such as neurons, glia, and the like. Among those agents that are preferred are neurotrophic and
25   neuritogenic factors that are similar to naturally occurring nerve growth promoting substances or "growth factors." As used herein, the term "growth factor" is synonomous with the term "trophic factor." Among the preferred neurologic agents are trophic factors such as
30   gangliosides, phosphatidylserine (PS), nerve growth factor (NGF), brain-derived neurotrophic factor, fibroblast growth factors, insulin, insulin-like growth factors, ciliary neurotrophic factor, neurotropin 3, glia-derived nexin, cholinergic enhancing factors, cholinesterase
35   inhibitors, platelet derived growth factors, alpha platelet derived growth factor, transforming growth factor beta, and other growth factors which may be capable of

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acting in the brain. GM-1 ganglioside and nerve growth factor (NGF) are particularly preferred. One or several neurologic substances may be combined together.

The neurologic agent may further be capable of antiviral, antibacterial, antineoplastic, antiparasitic, anti-inflammatory, and/or antifungal activity. The agent may also be a substance which is capable of acting as a neurotransmitter, neuromodulator, nootropic, hormone, hormone releasing factor, or hormone receptor agonist or antagonist. The agent may also be an activator or inhibitor of a specific enzyme, an antioxidant, a free radical scavenger, a metal chelating agent, or an agent which alters the activity of ion channels of brain cell membranes, for example, nimodipine. The agent may further be any substance which is capable of acting as a stimulant, sedative, hypnotic, analgesic, anticonvulsant, antiemetic, anxiolytic, antidepressant, tranquilizer, cognition enhancer, and/or narcotic antagonist or agonist. Further, the neurologic agent may be any substance found to be deficient in conjunction with the brain disorder being treated or prevented, for example, nutrients such as glucose, ketone bodies, and the like, or metabolic precursors such as lecithin (phosphatidylcholine), choline or acetyl coenzyme A for producing neurotransmitters for the treatment of Alzheimer's disease.

A preferred embodiment of the therapeutic composition is the combination of an effective amount of nerve growth factor (NGF) protein with an appropriate amount of GM-1 ganglioside in a pharmaceutically-acceptable liquid carrier. The GM-1 may function not only as an active ingredient of the composition, but may also provide lipid vesicles and micelles which may facilitate the delivery of the medication by means of the peripheral olfactory neural pathway to the brain. GM-1 is thought to act synergistically with nerve growth factor (NGF) to protect neurons and promote nerve regeneration and repair. See Gorio et al., Neuroscience 8:417-429 (1983).

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For diagnosis of brain diseases or disorders, it is preferred that the neurologic agent is a diagnostic agent, for example, polyclonal or monoclonal antibodies which are capable of detecting substructures or biochemical markers characteristic of the disease or disorder. It has been demonstrated that certain central neurons, especially those neurons of the CNS with axons projecting outside of the blood-brain barrier, are capable of taking up immunoglobulins from the periphery by retrograde axonal transport. See Fabian, R.H. and G. Petroff, Neurology 37:1780-1784 (1987); and Fabian, R.H., Neurology 40:419-422 (1990). Preferably the antibody is monoclonal. Such diagnostic antibodies may be labeled with any labeling agent which may be suitable according to the invention. Suitable labeling agents include, for example, technetium-99m, 123-I, gold or other electron dense particles, positron emitters, and the like. These labels may be detected using appropriate imaging techniques such as single photon emission computed tomography (SPECT), medical resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT), and the like, depending upon the type of label used. Chemical reagents which have an affinity for or are capable of detecting diseased cells or pathologic structures, features, or biochemical markers, including receptors, may also be used as the diagnostic agent. For example, 123-I-quinuclidinyl benzilate (QNB) which binds to muscarinic acetylcholine receptors in the brain and may be imaged with SPECT, and ^{11}C-nicotine which binds to nicotinic acetylcholine receptors and may be imaged with PET may be used as diagnostic chemical reagents.

A preferred embodiment of a diagnostic composition useful for the diagnosis of Alzheimer's disease comprises an antibody selectively reactive with molecular species ("tangletopes") associated with Alzheimer's disease, and most preferably with glycolipid, sulfolipid, phospholipid or phosphoprotein antigens. A

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preferred composition comprises monoclonal antibody TLE-
41, GLE-17, or A2B5.   A highly preferred diagnostic
composition comprises monoclonal antibody A2B5 labeled
with a labeling agent such as technetium-99m, in
5   combination with a pharmaceutically-acceptable liquid
carrier.

        The invention is also directed to a method of
diagnosing dependency to addicting substances such as
caffeine, nicotine, and cocaine, cannabinoids such as
10   marihuana, opiates such as heroin, and other narcotics.
According to this method, a labeled receptor active
neurologic agent may be intranasally administered.   The
receptor active agent is preferably capable of binding
with receptors for the particular addicting substance
15   (i.e., heroin, nicotine) for which addiction is being
examined.   Labeled receptors may then be detected using an
appropriate imaging technique.   The number of receptors
bound by the labeled agent may also be assessed and/or
quantified to evaluate the existence of and/or level of
20   addiction.   For example, an opiate receptor antagonist
labeled   with   technetium-99m   may   be   administered
intranasally and imaged to assess and/or measure the level
of opiate addiction according· to the quantity of labeled
receptors.

25   In addition to diagnosing dependency on addicting
substances, the invention also provides a method of
treatment of such dependency.   A therapeutic neurologic
agent may be administered intranasally, the neurologic
agent being a receptor active agent capable of binding to
30   a receptor for an addicting substance such as caffeine,
nicotine, or heroin, cocaine, opiates and other narcotics.
It is preferred that the agent is capable of altering or
blocking the receptor so as to interfere with the action
of such addictive substances.

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Detailed Description of the Invention

The method of the present invention administers a neurologic agent to the nasal cavity of a human or other mammal for the testing of potential therapeutic agents against brain disease and for the treatment and/or diagnosis of brain disorders such as Alzheimer's disease, Parkinson's disease, AIDS, brain tumors, schizophrenia, affective disorders such as depression and mania, anxiety disorders, dependency on addicting substances, nerve damage from cerebrovascular disorders such as stroke, or brain changes associated with aging. In particular, the method delivers a neurologic agent to diseased areas of the brain by means of the olfactory neural pathway. The method may employ a pharmaceutical composition capable of transporting the neurologic agent to diseased neurons of the brain.

The method of the invention may achieve delivery of neurologic substances to afflicted areas of the brain through transneuronal retrograde and anterograde transport mechanisms. Delivery of neurologic agents to the brain by that transport system may be achieved in several ways. One technique comprises delivering the neurologic agent alone to the nasal cavity. In this instance, the chemical characteristics of the agent itself facilitate its transport to diseased neurons in the brain. Alternatively, the agent may be combined with other substances that assist in transporting the agent to sites of damaged neurons. It is preferred that auxiliary substances are capable of delivering the agent to peripheral sensory neurons and/or along neural pathways to dysfunctioning areas of the brain. It is further preferred that the peripheral nerve cells of the olfactory neural pathway be utilized in order to deliver the neurologic agent to damaged neurons in those regions of the brain that are connected to the olfactory bulb.

The neurologic agent that is administered by the method of the invention may be generally absorbed into the

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bloodstream and the neural pathway of the mammal. It is
preferred that the agent exhibits minimal effects
systemically. For treatment and/or prophylaxis, it is
preferred that a large enough quantity of the agent be
5 applied in non-toxic levels in order to provide an
effective level of activity within the neural system
against the brain disease. It is further preferred that
the neurologic agent promote nerve cell growth and
survival or augment the activity of functioning cells
10 including enhancing the synthesis of neurotransmitter
substances. Among those agents that are preferred are
neurotrophic and neuritogenic factors that are similar to
or the same as nerve growth promoting substances that are
naturally occurring in the nervous system of a mammal.
15 The agent may be administered to the nasal cavity alone or
in combination with other neurologic agents. The agent
may be combined with a carrier and/or other adjuvants to
form a pharmaceutical composition. Trophic factors are
among the preferred neurologic agents according to the
20 invention.   Preferred   trophic   factors   include
gangliosides,   nerve   growth   factor   (NGF),
phosphatidylserine   (PS),   brain-derived neurotrophic
factor, fibroblast growth factors (FGF) such as basic
fibroblast growth factors (bFGF) and heparin-activated
25 acid FGF, insulin, insulin-like growth factors, ciliary
neurotrophic factor, neurotropin 3, glia-derived nexin,
and   cholinergic   enhancing   factors   such   as
p h o s p h o e t h a n o l a m i n e ,   L - a c e t y l c a r n i t i n e ,
cholineacetyltransferase development factor (CDF) and
30 thyroid hormone T.3, cholinesterase inhibitors such as
tetrahydroaminoacridine and heptylphyostigmine, platelet
derived growth factors, alpha platelet derived growth
factor, transforming growth factor beta, and other growth
factors that may be capable of acting in the brain. Among
35 those agents that are particularly preferred are GM-1
ganglioside and nerve growth factor (NGF).

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The neurologic agent may further be capable of antiviral, antibacterial, antineoplastic, antiparasitic, anti-inflammatory, and/or antifungal activity. The agent may be a substance which is capable of acting as a neurotransmitter, neuromodulator, nootropic, hormone, hormone releasing factor, or hormone receptor agonist or antagonist. The agent may further be any substance which may be capable of acting as a stimulant, sedative, hypnotic, analgesic, anticonvulsant, antiemetic, anxiolytic, antidepressant, tranquilizer, cognition enhancer, and/or narcotic antagonist or agonist. Additionally, the neurologic agent may be a substance found to be deficient for the brain disorder or disease being treated or prevented. For example, potential agents include nutrients such as glucose, ketone bodies and the like, or metabolic precursors such as lecithin (phosphatidylcholine), choline, acetyl coenzyme A, and the like, for producing neurotransmitter substances useful in the treatment of Alzheimer's disease. The agent may also be an activator or inhibitor of a specific enzyme, an antioxidant, a free radical scavenger, a metal chelating agent, or an agent which alters the activity of ion channels of brain cell membranes, for example, nimodipine.

The method of the invention delivers the neurologic agent to the nasal cavity of a mammal. It is preferred that the agent be delivered to the olfactory area in the upper third of the nasal cavity and particularly to the olfactory neuroepithelium in order to promote transport of the agent into the peripheral olfactory neurons rather than the capillaries within the respiratory epithelium. Located high in the vault of the nose, the olfactory area is the only area of the body in which an extension of the central nervous system comes into contact with the environment. Bois, et al., Fundamentals of Otolaryngology, page 184, W.B. Saunders Co., Philadelphia (1989). The invention prefers the transport of neurologic agents to the brain by means of

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the nervous system instead of the circulatory system so
that potentially therapeutic and/or diagnostic agents that
are unable to cross the blood-brain barrier from the
bloodstream into the brain may be delivered to damaged
5   neurons in the brain.

       It is preferred that the neurologic agent is
capable of at least partially dissolving in the fluids
that are secreted by the mucous membrane that surround the
cilia of the olfactory receptor cells of the olfactory
10   epithelium in order to be absorbed into the olfactory
neurons. Alternatively, the invention may combine the
agent with a carrier and/or other substances that foster
dissolution of the agent within nasal secretions.
Potential adjuvants include GM-1, phosphatidylserine (PS),
15   and emulsifiers such as polysorbate 80.

       To further facilitate the transport of the
neurologic agent into the olfactory system, the method of
the present invention may combine the agent with
substances that enhance the absorption of the agent
20   through the olfactory epithelium. It is preferred that
the additives promote the absorption of the agent into the
peripheral olfactory receptor cells. These peripheral
neurons provide a direct connection between the brain and
the outside environment due to their role in odor
25   detection.

       Optionally, drug solubilizers may be combined
with the agent to improve solubility of the neurologic
agent and/or help prevent disruption of nasal membranes
which may be caused by application of other additive
30   substances, for example, lipophilic odorants. Preferred
drug solubilizers include amorphous mixtures of
c y c l o d e s t r i n   d e r i v a t i v e s   s u c h   a s
hydroxypropylcylodextrins. See, for example, Pitha, et
al., _Life Sciences_ 43:493-502 (1988), the disclosure of
35   which is incorporated by reference herein.

       The olfactory receptor cells are bipolar neurons
with swellings covered by hairlike cilia which project

into the nasal cavity. At the other end, axons from these cells collect into aggregates and enter the cranial cavity at the roof of the nose. It is preferred that the neurologic agent is lipophilic in order to promote

5 absorption into the olfactory neurons and through the olfactory epithelium. Among those therapeutic neurologic agents that are lipophilic are gangliosides, for example GM-1, and phospholipids, for example phosphatidylserine (PS). Alternatively, the neurologic agent may be combined

10 with a carrier and/or other substances that enhance the absorption of the agent into the olfactory neurons. Among the supplementary substances that are preferred are lipophilic substances such as gangliosides, for example GM-1, and phospholipids such as phosphatidylserine (PS).

15 Uptake of non-lipophilic neurologic agents such as nerve growth factor (NGF) may be enhanced by the combination with a lipophilic substance. Other lipophilic substances that may enhance delivery of the neurologic agent across the nasal mucusa include bile salts such as sodium

20 deoxycholate, and detergent-like adjuvants including, for example, polysorbate 80 such as Tween™, octoxynol such as Triton™ X-100, and sodium tauro-24,25-dihydrofusidate (STDHF). See Lee, et al., Biopharm., April 1988 issue:30-37 (1988).

25   In one embodiment of the method of the invention, the neurologic agent may be combined with micelles comprised of lipophilic substances. Such micelles may modify the permeability of the nasal membrane to enhance absorption of the agent. Among the lipophilic micelles

30 that are preferred are gangliosides, particularly GM-1 ganglioside, and phospholipids, particularly phosphatidylserine (PS). Bile salts and their derivatives and detergent-like adjuvants may also be added as micelle substances. The neurologic agent may be combined with one

35 or several types of micelle substances, and may further be contained within the micelles or associate with their surface.

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Alternatively, the neurologic agent may be combined with liposomes (lipid vesicles) to enhance absorption of the neurologic agent into the olfactory system. Preferred liposome additives are those substances which provide vesicles which are readily soluble in fats and which are bounded by lipid with an internal cavity containing a liquid such as water. Preferably the neurologic agent is contained or dissolved within the liposome or associated with its surface. Among those liposome substances that are preferred are phospholipids, such as phosphatidylserine (PS), and gangliosides, such as GM-1. For methods to make phospholipid vesicles, see for example, U.S. Patent 4,921,706 to Roberts, et al., and U.S. Patent 4,895,452 to Yiournas, et al. Bile salts and their derivatives and detergent-like adjuvants may also be added as liposome substances.

Once the agent has crossed the nasal epithelium, the invention further provides for transport of the neurologic agent along the olfactory neural pathway. The agent itself may be capable of movement within the olfactory system. In particular, neurotrophic and neuritogenic substances have demonstrated ready incorporation into nerve cell membranes and an affinity for nerve cell receptor sites. Indications are that these substances are naturally synthesized in tissues in response to neural stimulation and that they subsequently bind to receptors on neurons where they act as nerve growth promoting factors.

Alternatively, the neurologic agent may be combined with substances that possess neurotrophic or neurotogenic properties which, in turn, may assist in transporting the agent to sites of nerve cell damage.

Optionally, an odorant agent may be combined with the neurologic agent to provide an odoriferous sensation, and/or to encourage inhalation of the intranasal preparation to enhance delivery of the active neurologic agent to the olfactory neuroepithelium. The odoriferous

sensation provided by the odorant agent may be pleasant, obnoxious, or otherwise malodorous. The odorant receptor neurons are localized to the olfactory epithelium which, in humans, occupies only a few square centimeters in the

5   upper part of the nasal cavity. The cilia of the olfactory neuronal dendrites which contain the receptors are fairly long (about 30-200 um). A 10-30 um layer of mucus envelops the cilia which the odorant agent must penetrate to reach the receptors. See Snyder, et al., _J._

10   _Biol. Chem_ 263:13972-13974 (1988). Use of a lipophilic odorant agent having moderate to high affinity for odorant binding protein (OBP) is preferred. OBP has an affinity for small lipophilic molecules found in nasal secretions and may act as a carrier to enhance the transport of a

15   lipophilic odorant substance and active neurologic agent to the olfactory receptor neurons. It is also preferred that an odorant agent is capable of associating with lipophilic additives such as liposomes and micelles within the preparation to further enhance delivery of the

20   neurologic agent by means of OBP to the olfactory neuroepithelium. OBP may also bind directly to lipophilic neurologic agents to enhance transport of the neurologic agent to olfactory neural receptors.

Suitable odorants having a high affinity for OBP

25   include terpenoids such as cetralva and citronellol, aldehydes such as amyl cinnamaldehyde and hexyl cinnamaldehyde, esters such as octyl isovalerate, jasmines such as ClS-jasmine and jasmal, and musk 89. Other suitable odorant agents include those which may be capable

30   of stimulating odorant-sensitive enzymes such as adenylate cyclase and guanylate cyclase, or which may be capable of modifying ion channels within the olfactory system to enhance absorption of the neurologic agent.

The invention also provides a means for the

35   prevention of brain disorders particularly in cases where the causative factor enters the brain through olfactory neurons. It is preferred that prophylactic treatments be

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employed where evidence indicates neuronal degeneration in the olfactory neurons as in the case of Alzheimer's disease and other related brain disorders. Prophylactic treatment of brain disease may involve the direct or

5   indirect application of neurologic therapeutic agents to the olfactory epithelium. Such agents may be absorbed into the peripheral olfactory nerve cells to protect those neurons from damage from neurotoxins and other insults and thereby prevent the spread of a disease-causing agent into

10 other areas of the olfactory neural pathway and treat and/or prevent the loss of smell which may be associated with neurodegenerative diseases and aging. Although part of the central nervous system, the neurons of the olfactory epithelium are capable of proliferating

15 throughout adult life. See Graziadei, P.P.C. and Monti Graziadei, G.A., _J. Neurocytol._ 8:1-18 (1979). As in the foregoing methods of treatment, prophylactic therapies may apply the neurologic agent alone or in combination with a carrier, other neurologic agents, and/or other substances

20 that may enhance the absorption of the agent into the olfactory neurons. Potential neurologic agents include trophic factors such as gangliosides, nerve growth factor (NGF), phosphatidylserine (PS), brain-derived neurotrophic factor, fibroblast growth factors (FGF) such as basic

25 fibroblast growth factors (bFGF) and heparin-activated acid FGF, insulin, insulin-like growth factors, transforming growth factor beta, ciliary neurotrophic factor, neurotropin 3, glia-derived nexin, cholinergic enhancing factors such as phosphoethanolamine, CDF, and

30 thyroid hormone T.3, cholinesterase inhibitors such as tetrahydroaminoacridine and heptylphyostigmine, platelet derived growth factors, alpha platelet derived growth factor, transforming growth factor beta, and other growth factors which may be capable of acting within the brain.

35 GM-1 ganglioside and nerve growth factor (NGF) are among those agents that are particularly preferred for prophylactic treatment of brain disorders.

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Potential neurologic agents useful in the prevention and/or treatment of brain disease include those agents which may be capable of antiviral, antibacterial, antineoplastic, antiparasitic, anti-inflammatory, and/or
5   antifungal activity, and those agents which may be capable of acting as a neurotransmitter, neuromodulator, nootropic, hormone, hormone releasing factor or hormone receptor agonist or antagonist. Other potential agents include substances which may be capable of acting as a
10   stimulant, sedative, hypnotic, analgesic, anticonvulsant, antiemetic, anxiolytic, antidepressant, tranquilizer, cognition enhancer and/or narcotic antagonist or agonist. The agent may also be an activator or inhibitor of a specific enzyme, an antioxidant, a free radical scavenger,
15   a metal chelating agent, or an agent which may be capable of altering the activity of ion channels of brain cell membranes, for example, nimodipine. The neurologic agent may further be a substance that is found to be deficient for the brain disorder or disease being treated or
20   prevented, for example, nutrients such as glucose, ketone bodies and the like, or metabolic precursors for producing neurotransmitter substances such as lecithin (phosphatidylcholine), choline, and acetyl coenzyme A, which are precursors for neurotransmitters useful in the
25   treatment of Alzheimer's disease.

         To deliver the neurologic agent to the olfactory neurons, the agent alone or in combination with other substances as a pharmaceutical composition may be administered to the olfactory area located in the upper
30   third of the nasal cavity. The composition may be dispensed intranasally as a powdered or liquid nasal spray, nose drops, a gel or ointment, through a tube or catheter, by syringe, by packtail, by pledget, or by submucosal infusion.

35   As an alternative to administering the neurologic agent directly into the nasal passage, the composition may first be administered to the eye as eye drops. Tears

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drain through the nasolacrimal ducts into the nasal cavity and become mixed with nasal secretions. Lactoferrin, a substance in tears and the nasal mucosa, has been identified in the plaques and tangles of Alzheimer's disease. See, Osmond, et al., Neurobiology of Aging 11:284 (1990). It is preferred that eye drops containing the neurologic agent are administered to the eye, and the liquid allowed to drain through the nasolacrimal ducts into the nasal cavity and mix with nasal secretions, wherein the agent is delivered to the brain by means of the olfactory neural pathway according to the method of the invention.

The optimal concentration of the active neurologic agent will necessarily depend upon the specific neurologic agent used, the characteristics of the patient and the nature of the disease or condition for which the treatment is to be used. The neurologic agent may be used alone or in combination with other substances as a pharmaceutical composition at such concentrations as 30μM GM-1 ganglioside, 3nM nerve growth factor (NGF), and 300μM phosphatidylserine (PS). These concentrations are intended only as examples and do not exclude the use of other concentrations.

The invention is further directed to a pharmaceutical composition comprising an amount of a neurologic agent which is effective in treating or preventing brain disorders in a mammal, when administered thereto, in combination with a pharmaceutically-acceptable vehicle such as a liquid or powdered carrier and/or various optional adjuvants. The pharmaceutical composition is particularly useful for treating patients with Alzheimer's disease.

The neurologic therapeutic agent of the pharmaceutical composition may be any substance that promotes the survival of nerve cells and other normal brain cells and prevents their further loss. It is preferred that the agent has minimal systemic effects and

augments the activity of naturally occurring nerve growth
promoting factors. Preferably, the agent is capable of
acting as a nerve growth promoting factor to prevent
degeneration of neurons, to induce regrowth of dendrites
5   and axons, and to augment the function of remaining
neurons such as synthesizing neurotransmitter substances.
Among the neurologic agents that are preferred are trophic
factors such as nerve growth factor (NGF), gangliosides,
phosphatidylserine (PS), brain-derived neurotrophic
10   factor, fibroblast growth factors (FGF) such as basic
fibroblast growth factors (bFGF) and heparin-activated
acidic FGF, insulin, insulin-like growth factors,
platelet-derived growth factors, ciliary neurotrophic
factor, neurotropin 3, glia-derived nexin, transforming
15   growth factor beta, and cholinergic enhancing factors such
as L-acetylcarnitine, phosphoethanolamine, thyroid hormone
T3, and cholineacetyltransferase development factor (CDF),
cholinesterase inhibitors such as tetrahydroaminoacridine
and heptylphysostigmine, alpha platelet derived growth
20   factor, and other growth factors that may be capable of
acting within the brain.

        The composition may comprise a neurologic agent
which may be capable of antiviral, antibacterial,
antineoplastic, antiparasitic, anti-inflammatory, and/or
25   antifungal activity. The agent may also be a substance
that may be capable of acting as a neurotransmitter,
neuromodulator, nootropic, hormone, hormone releasing
factor, or hormone receptor agonist or antagonist. The
agent may further be any substance which may be capable of
30   acting as a stimulant, sedative, hypnotic, analgesic,
anticonvulsant, antiemetic, anxiolytic, antidepressant,
tranquilizer, cognition enhancer, narcotic antagonist or
agonist including agents such as carbamazepine which may
be useful in the treatment of substance abuse. The agent
35   may also be an activator or inhibitor of a specific
enzyme, an antioxidant, a free radical scavenger, a metal
chelating agent, or an agent which may be capable of

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altering the activity of ion channels of brain cell
membranes, for example, nimodipine. The agent may also be
a substance found to be deficient for the brain disorder
or disease being treated or prevented, for example,
nutrients such as glucose, ketone bodies and the like, or
metabolic   precursors   such   as   lecithin
(phosphatidylcholine), choline, acetyl coenzyme A and the
like, for producing neurotransmitter substances useful in
the treatment of Alzheimer's disease and other brain
disorders.

      The carrier of the composition may be any
material which is otherwise pharmaceutically-acceptable
and compatible with the active ingredients of the
composition.   Where the carrier is a liquid, it is
preferred that the carrier is within the range of pH 4.5-
8.5.   Where the carrier is in powdered form, it is
preferred that the carrier is also within an acceptable
non-toxic pH range.

      Among the optional substances that may be
combined with the neurologic agent in the pharmaceutical
composition are lipophilic substances that may enhance
absorption of the agent across the nasal membrane and
delivery to the brain by means of the olfactory neural
pathway.   The neurologic agent may be mixed with a
lipophilic adjuvant alone or in combination with a
carrier.   Among the preferred lipophilic substances are
gangliosides such as GM-1 and phospholipids such as
phosphatidylserine (PS).   One or several lipophilic
adjuvants may be combined with the agent. It is preferred
that the lipophilic adjuvant be added as micelles or
liposomes.

      The pharmaceutical composition may also include
odorant substances to provide an odoriferous sensation
and/or enhance inhalation of the composition.   Odorant
agents, preferably with an affinity for odorant binding
protein (OBP), may also be included to augment the
transport of the neurologic agent to olfactory receptor

neurons.   Where lipophilic neurologic agents and/or
substances such as liposomes and micelles are included in
the composition, it is preferred that the odorant agent
have an affinity for the lipophilic substance. Among the
preferred odorant agents are terpenoids such as cetralva
and citronellol, aldehydes such as amyl cinnamaldehyde and
hexyl cinnamaldehyde, esters such as octyl isovalerate,
and jasmines such as C1S-jasmine and jasmal, and musk 89.
The odoriferous sensation provided by the odorant agent
may be pleasant, obnoxious or otherwise malodorous.

        The pharmaceutical composition may be formulated
as a powder, granules, solution, ointment, cream, aerosol,
powder, or drops.   The solution may be sterile and
otherwise suitable for administration by injection or
other means.   In addition to the neurologic agent, the
solution may contain appropriate adjuvants, buffers,
preservatives and salts. The powder or granular forms of
the pharmaceutical composition may be combined with a
solution and with diluting, dispersing and/or surface
active agents. Solutions such as nose drops or eye drops
may contain antioxidants, buffers, and the like.

        · A preferred embodiment of the pharmaceutical
composition of the invention is a micellar and/or
liposomal suspension of GM-1 ganglioside with an effective
amount of nerve growth factor (NGF) combined with
appropriate amounts of an odorant such as cetralva, a
stabilizer such as microcrystalline cellulose, a
suspending agent such as carboxymethyl cellulose or
hydroxypropyl methylcellulose, an emulsifier such as
polysorbate 80, a preservative such as benzalkonium
chloride, an antimicrobial such as phenylethyl alcohol,
and a thickener such as dextrose.

        The present invention for a method of
administering neurologic agents useful in the treatment of
brain disorders such as Alzheimer's disease presents
several advantages over currently available methods.

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The method of the present invention prefers the olfactory neural pathway rather than the bloodstream to deliver agents useful for the treatment of brain disorders such as Alzheimer's disease directly to the brain. Use of the olfactory system to transport a neurologic agent to the brain bypasses the blood-brain barrier so that medications like nerve growth factor (NGF), a protein that cannot normally cross that barrier, can be delivered directly to the brain. Although the agent that is administered may be absorbed into the bloodstream as well as the olfactory neural pathway, the agent provides minimal effects systemically. In addition, the invention provides for delivery of a more concentrated level of the agent to neural cells since the agent does not become diluted in fluids present in the bloodstream. As such, the invention provides an improved method of testing potential therapeutic agents against brain disease and of treating neurodegenerative disorders.

The method provides an advantage by virtue of the intranasal administration of the medication. The olfactory system provides a direct connection between the outside environment and the brain thus providing quick and ready delivery of neurologic agents for treatment of neurologic disorders. Moreover, the means of applying a pharmaceutical composition intranasally can be in a variety of forms such as a powder, spray or nose drops which obviates intravenous or intramuscular injections and simplifies the administration of therapeutic medications. As such, the method of the present invention is an improvement over present methods of direct administration of neurologic therapeutic agents, such as the intracerebroventricular pump.

The application of a neurologic therapeutic agent to the nasal epithelium also helps prevent the spread of certain brain disorders by directly treating peripheral olfactory neurons that are injured by neurotoxins and other insults. Prophylactic treatment of these outlying

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nerve cells helps preclude the entrance of disease-causing
agents into the brain. This method of treatment is
particularly beneficial in cases of Alzheimer's disease
where an environmental factor, suspected of being one of
the causative agents of the disease, is thought to enter
the brain through the olfactory pathway. Application of
a neurologic therapeutic agent to the olfactory sensory.
neurons also in part treats and/or prevents the loss of
smell which may be associated with neurodegenerative
diseases and ordinary aging. Neurons of the olfactory
epithelium are capable of proliferation throughout the
adult life. See Graziadei, P.P.C. and Monti Graziadei,
G.A., J. Neurocytol. 8:1-18 (1979).
        Another advantage of the invention is that it
provides delivery of neurologic agents solely to those
areas of the brain affected by disease while avoiding
unwanted treatment of brain regions which are free of the
disease. The method of the invention employs a neurologic
agent or other substance that has an affinity for neuron
receptor sites in order to facilitate delivery of the
agent directly to the brain through the olfactory
epithelium.
        The invention also provides a means for
delivering diagnostic neurologic agents to the nasal
neuroepithelium, olfactory bulb and other brain
structures. The invention is especially useful for the
delivery of diagnostic agents, such as antibodies, which
do not easily cross the blood-brain barrier. The
invention is also advantageous because it delivers the
diagnostic agent principally to those areas of the brain
affected by disease.
        It is preferred that the diagnostic neurologic
agent is capable of detecting substructures associated
with Alzheimer's disease, Parkinson's disease, AIDS, brain
tumors, cerebrovascular disorders, schizophrenia,
affective disorders, psychiatric illness, anxiety
disorders, aging, dependency on addicting substances, or

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other neurologic disorder or disease. Chemical reagents
which have an affinity for or may be capable of detecting
diseased cells or pathologic structures, features or
biochemical markers, including receptors, may be used as
5   diagnostic agents. An example of a diagnostic chemical
agent is basic fibroblast growth factor (bFGF) which binds
to pathologic structures in the brains of patients with
Alzheimer's disease. See T. Kato, et al., Neurobiology of
Aging 11:268 (1990). The bFGF may be labeled and imaged
10   with a variety of imaging techniques. An example of a
receptor-based diagnostic agent (receptor ligand) is 123-
I-quinuclidinyl benzilate (QNB) which is capable of
binding to muscarinic acetylcholine receptors in the brain
and can be imaged with SPECT. Other examples of
15   diagnostic agents are 11C-(2) deoxyglucose, 18-fluoro-
deoxyglucose, ^{133}Xe and ^{11}C-nicotine. It is preferred that
antibodies that are used as diagnostic neurologic agents
are capable of detecting antigens which are characteristic
of the brain disease or disorder. The antibody may be
20   polyclonal or monoclonal. Preferably, the antibody is
monoclonal.

It is preferred that antibodies used as agents
for the diagnosis of Alzheimer's disease are selectively
reactive with glycolipid, sulfolipid, phospholipid, or
25   phosphoprotein antigens. More specifically, it is
preferred that the antibodies are selectively reactive
with "tangletopes" which are a molecular species that is
characteristic of, and specific for, the diagnosis of that
brain disease. A "tangletope" in the context of the
30   invention refers to antigenic phosphate- or sulfate-
containing lipid and/or protein compounds, epitopes, or
haptens, and to antigenic markers such as molecular
substructures, that are associated with Alzheimer's
disease. Alzheimer's neurofibrillary tangles are known to
35   contain several phosphoproteins including phosphorylated
tau. Highly preferred antibodies for use in the diagnosis
of Alzheimer's disease are the monoclonal antibodies A2B5,

TLE-41, GLE-17, and any monoclonal antibody against a mammalian sulfatide such as bovine sulfatide, or against protein phosphate epitopes. For a discussion regarding A2B5, see U.S. patent application Serial No. 07/398,079 filed August 24, 1989, the disclosure of which is incorporated by reference herein. See also Clements, et al., _Alzheimer Disease and Assoc. Disorders_ 4:35-42 (1990). Also highly preferred for use in the diagnosis of Alzheimer's disease is any monoclonal antibody against protein phosphate epitopes, including monoclonal antibody A2B5 which reactivity with phosphoproteins was recently discovered by Applicant.

The hybridomas producing monoclonal antibodies TLE-41 and GLE-17 have been deposited with American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland, and have been assigned the following ATCC accession numbers: the hybridoma for TLE-41 is HB-10521, and the hybridoma for GLE-17 is HB-10520. Cultures of these deposited hybridomas will be made available to the public upon the grant of a patent based upon the present application. It is to be understood that the availability of a deposit does not constitute a license to practice the subject invention in derogation of patent rights granted by the United States Government.

Besides phosphorylated tau, plaques and tangles of Alzheimer's disease are also believed to contain certain antigens including ubiquitin, microtubule associated protein-2 (MAP-2), phosphorylated MAP-5, amyloid beta protein, A-68, heparin sulfate proteoglycans, lactoferrin, and phosphorylated tau. Consequently, any antibody which may be capable of activity against those antigens would be suitable as a diagnostic agent according to the invention. Examples of useful antibodies include those which are anti-ubiquitin, anti-MAP-2, anti-amyloid beta protein, and so forth. Highly preferred is the antibody ALZ-50. See, for example, P. Davies, _J. Amer. Med. Assoc._ 263: 2907-2910 (1990).

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Various techniques are employed to produce hybridomas capable of secreting monoclonal antibodies that are selectively reactive with circulating tangletopes, e.g., phospholipid, glycolipid, sulfolipid and

5   phosphoprotein epitopes which reflect the tangletope abnormalities characteristic of Alzheimer's disease. Such techniques for antibody preparation are set forth in M. M. Rapport and Y. Huang in _Advances in Experimental Medicine and Biology_, Vol. 174, R. W. Ledeen, et al., eds., pp. 15-

10   25 (1984), and in G. S. Eisenbarth, et al., _Proc. Natl. Acad. Sci. USA_ 76: 4913 (1979), the disclosures of which are incorporated by reference herein.

       Monoclonal antibody A2B5 is a murine IgM produced by a hybridoma that is commercially available from

15   American Type Culture Collection (ATCC No. CRL1520). This antibody is secreted by a cloned hybridoma formed by the fusion of the murine myeloma P3X63 Ag8 with spleen cells derived from a BALB/c mouse immunized against chick embryo retina cells. Monoclonal antibody A2B5 is known to bind

20   to neurofibrillary tangles and senile plaques characteristic of Alzheimer's disease. This antibody exhibits only minimal reactivity with G_{Q1b} ganglioside, the tetrasialic ganglioside present in normal adult brain gray matter, and has been reported to be primarily reactive

25   with the tetrasialic acid ganglioside G_{Q1c}. A2B5 has also been demonstrated to be reactive with sulfatide from human or bovine brain and certain base-labile glycolipids. Furthermore, immuno-TLC studies utilizing A2B5 have demonstrated that A2B5 binds to and detects the sulfated

30   glycolipid, sulfatide, from bovine brain. A2B5 also reacts with phosphoproteins such as phosvitin and casein, and with phospholipids such as dolichol phosphate by ELISA. A2B5 also reacts with a glycolipid, phospholipid or sulfolipid species from extracts of human brain,

35   Alzheimer's neurofibrillary tangles, and Alzheimer's cerebrospinal fluid (CSF), which migrate on the TLC test plates with the same retention time as bovine sulfatide on

TLC. Therefore, any antibody specific to the detection of these lipids or to phosphoproteins present in Alzheimer's neurofibrillary tangles or neuritic plaques may be used in the Alzheimer's disease detection method of the present invention.

Monoclonal antibody GLE-17 and TLE-41 are murine IgM antibodies that react with Alzheimer's neurofibrillary tangles and label Alzheimer's brain neurofibrillary tangles by immunohistochemistry. Monoclonal antibody TLE-41 has demonstrated reactivity with total lipid extract (TLE) of Alzheimer's cerebral cortex, with certain phosphoproteins such as casein by ELISA, and with human and bovine brain sulfatide by ELISA. Monoclonal antibody GLE-17 has demonstrated reactivity with a crude ganglioside fraction of Alzheimer's cerebral cortex. Although the antigens detected by these antibodies are not yet confirmed, the antigens are suspected as being a sulfolipid, glycolipid, phosphoprotein or phospholipid. Both antibodies, being capable of distinguishing Alzheimer's afflicted brain tissue from normal or non-demented brain tissue, may function as diagnostic agents for that disorder.

The detection of the presence of a characterizing tangletope includes either the use of a label directly bound to the diagnostic antibody agent, or the addition of a labeled second antibody which is reactive against the diagnostic antibody agent. The label may be any of a variety of well known and commonly used labels, for example, a radioactive, enzymatic, or fluorescent group. It is preferred that antibodies are labeled with a labeling agent such as technetium-99m, 123-I, gold or other electron dense particles, positron emitters, and the like. The labeled antibody may be detected using various imaging techniques, for example, single photon emission computed tomography (SPECT), medical resonance imaging (MRI), positron emission tomography (PET), computed

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tomography (CT), and the like. The method of detection is
matched with the type of label used.

A preferred composition useful in the diagnosis
of Alzheimer's disease comprises monoclonal antibody A2B5
5   labeled with technetium-99m or other suitable labeling
agent, in combination with a pharmaceutically-acceptable
liquid carrier.

The invention also provides a method to diagnose
an individual's dependence on addicting substances such as
10   alcohol and other chemical compounds, especially those
characterized by the popular press as drugs. Addicting
substances, for example, may include caffeine, nicotine,
and cocaine, cannabinoids such as marihuana, opiates such
as heroin, and other narcotics. The method is useful for
15   the delivery of labeled receptor active neurologic agents
which are capable of binding to neural receptors for a
particular chemical substance (i.e., heroin, nicotine).
Labeled receptors may then be detected using an
appropriate imaging technique. Further, the number of
20   receptors bound by the labeled agent, and the extent of
binding with respect to time and the concentration of the
labeled agent may also be assessed and/or quantified to
evaluate the level or extent of addiction. For example,
an opiate receptor antagonist labeled with technetium-99m
25   may be administered intranasally, imaged with SPECT, and
the extent of labeled receptor quantified to assess and/or
measure the level of opiate addiction. Similarly, ^{11}C-
nicotine may be administered intranasally, imaged with
PET, and the binding of nicotine to receptors quantified
30   to assess nicotine use and addiction and/or habituation in
smokers or those using other nicotine-containing products
or substances.

Examples of receptor active neurologic agents for
use in diagnosing dependence on addicting substances
35   include, for example, naloxone, propiram, nalorphine,
cyclazocine, methadone, MET-enkephalin, LEU-enkephalin,
beta-endorphin,   hexamethonium,   mecamylamine,

carbamazepine, and QNB. These agents may be labeled with any labeling agent which is suitable according to the invention. Labeling agents which may be used include technetium-99m, ^{11}C, ^{13}C, 123-I, gold or other dense

5 particles, positron emitters, and the like. These labels may be detected using appropriate imaging techniques such as single photon emission computed tomography (SPECT), medical resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT), and the like,

10 depending upon the type of label used.

The invention also provides a method of treating dependency on addicting substances. A therapeutic neurologic agent which is a receptor active agent capable of binding to a receptor for an addicting substance such

15 as caffeine, nicotine, or cocaine, cannabinoids such as marihuana, opiates such as heroin, and other narcotics may be administered intranasally according to the method of the invention. Preferably, the agent is capable of altering or blocking the neural receptor such that the

20 action and/or uptake of addicting substances is hindered and/or blocked. Receptor active agents capable of altering and/or blocking neural receptor sites include, for example, naloxone, propiram, nalorphine, cyclazocine, methadone, MET-enkephalin, LEU-enkephalin, beta-endorphin,

25 hexamethonium, mecamylamine, QNB, propranolol, phentolamine, pimozide, chlorpromazine, haloperidol, and reserpine, lithium, and carbamazepine, the latter three agents being capable of activity other than receptor effects. Compositions useful in the treatment of

30 dependency on addicting substances preferably comprise an amount of a receptor active agent effective to block receptors for the addicting substance in a pharmaceutically-acceptable liquid carrier. Agents may be further combined with a lipophilic adjuvant. Optionally,

35 odorant substances may be added to the composition. A preferred composition useful in the treatment of, for example, heroin addiction, is the combination of an amount

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of naloxone effective to block heroin receptors in the
brain, in combination with an appropriate amount of
phosphatidylserine to provide lipid vesicles and/or
micelles, in a pharmaceutically-acceptable liquid carrier.

5   Another method of treating dependency on
addicting substances according to the invention comprises
intranasally administering a therapeutic neurologic agent
which may be capable of modulating enzyme activity so as
to hinder and or block the action and/or uptake of

10   addicting substances. For example, alpha-methyltyrosine,
an inhibitor of tyrosine hydroxylase, may be administered
to reduce the effects of amphetamine, or carbamazepine may
be administered to reduce the effects of cocaine.

The invention will be described with reference to

15   various specific and preferred embodiments and techniques.
However, it should be understood that many variations and
modifications may be made while remaining within the
spirit and scope of the invention.

20   **EXAMPLE 1**

Formulations of Pharmaceutical Compositions

Active Ingredients
25
Group 1. 30µM GM-1 ganglioside (GM-1)

Group 2. 3nM nerve growth factor (NGF)

30   Group 3. 300µM phosphatidylserine (PS)

Group 4. 30µM GM-1
          3nM NGF

35   Group 5. 30µM GM-1
          300µM PS

Group 6. 3nM NGF
          300µM PS
40
Group 7. 30µM GM-1
          3nM NGF
          300µM PS

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To formulate an aqueous preparation of the pharmaceutical composition, one or more of the following substances and/or carriers may be combined with any one of the aforementioned groups of active ingredients: an odorant such as cetralva, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl methylcellulose, polysorbate 80, benzalkonium chloride, phenylethyl alcohol, and dextrose. The preparation is to be maintained at a pH between 4.5 - 8.5. The concentration of active ingredients may follow the guidelines set forth above, but does not exclude the use of other concentrations or active ingredients.

Alternatively, any one group of the aforementioned active ingredients may be combined with propellants such as trichloromonofluoromethane or dichlorodifluoromethane, and delivered by an aerosol spray or similar application means as a non-aqueous preparation. Oleic acid may be added to the mixture as a lubricant.

EXAMPLE 2

Formulating Micelles and/or Lipid Vesicles

The compositions of Example 1 may further contain micelles and/or lipid vesicles consisting of GM-1 ganglioside and/or phosphatidylserine (PS). To formulate micelles and/or lipid vesicles, the lipid may be exposed to sonication in the aqueous solution of the pharmaceutical composition. Lipid vesicles and/or micelles formed by this procedure may contain in their interior or associated with their surface, other active ingredients such as NGF and facilitate the delivery of these agents into the brain through the olfactory neural pathway.

EXAMPLE 3

Preparation of Monoclonal Antibodies GLE-17 and TLE-41

A number of monoclonal antibodies (MABs) were prepared as potential diagnostic agents for neurologic disorders such as Alzheimer's disease. Two of these MABs, GLE-17 and TLE-41, were prepared as follows:

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Frontal and temporal cortex material with neuropathologically confirmed Alzheimer's disease was homogenized in three volumes of distilled water. Chloroform and methanol were added to the homogenate to
5   give a 4:8:3 ratio of chloroform:methanol:water and the mixture was stirred overnight. Centrifugation yielded a soluble fraction or total lipid extract (TLE). A portion of the TLE was diluted further with water to yield a 4:8:5.6 mixture which partitioned into organic and aqueous
10   phases. The aqueous phase contained most of the gangliosides and was referred to as the ganglioside lipid extract (GLE).

The TLE and GLE fractions were dried down separately and redissolved in water. They were then
15   coated by air drying onto Escherichia coli which had previously been stripped using a series of extractions with acid and acetone. Bacteria coated with either TLE or GLE were then used as immunogens. MABs were prepared in mice and screened against immunogen originally.
20   Subsequent screening was performed by immunofluorescence against Alzheimer's tangle-bearing neurons and by ELISA against TLE and GLE.

Monoclonal antibodies GLE-17 and TLE-41 are IgM MABs which were found to be reactive with neurofibrillary
25   tangles of Alzheimer's disease. Accordingly, both MABs are capable of acting as diagnostic agents, being capable of distinguishing Alzheimer's brain tissue from normal or non-demented brain tissue. Both MABs were also reactive with brain sulfatide. TLE-41 was also reactive with
30   certain phosphoproteins, such as casein, by ELISA.

For further description of methods of coating bacterial membranes with antigens for the preparation of monoclonal antibodies, see Galanos, et al., European Journal of Biochemistry 24: 116-122 (1971), and Young, et
35   al., Journal of Experimental Medicine 150: 1008-1019 (1979).

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WHAT IS CLAIMED:

1.   A pharmaceutical composition for use in administering a neurologic therapeutic agent to the nasal cavity of a mammal for delivery of the agent to the brain of the mammal, comprising: an effective amount of the agent for treating or preventing a brain disease or disorder in combination with a pharmaceutically-acceptable component, the agent or the component having properties that enable the agent to be absorbed through the nasal mucosa and transported by means of the olfactory neural pathway to the brain of the mammal.

2.   A composition according to claim 1 wherein the agent is capable of treating or preventing the loss of smell.

3.   A composition according to claim 1 wherein the agent is capable of providing antiviral, antibacterial, antineoplastic, antiparasitic, anti-inflammatory, antifungal, stimulant, sedative, hypnotic, analgesic, anticonvulsant, antiemetic, anxiolytic, antidepressant, tranquilizer, cognition enhancer, narcotic antagonist or agonist activity, or any combination of activity thereof.

4.   A composition according to claim 1 wherein the agent is a trophic factor.

5.   A composition according to claim 1 wherein the agent is capable of acting as a neurotransmitter, neuromodulator, nootropic, hormone, hormone releasing factor, hormone receptor agonist or antagonist, enzyme activator or inhibitor, antioxidant, free radical scavenger, metal chelating agent, or of altering the activity of ion channels.

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6.   A composition according to claim 1 wherein the component is an appropriate amount of lipophilic micelles or liposomes, odorant agent or any combination thereof.

7.   A composition according to claim 6 wherein the agent is contained within the micelles or liposomes.

8.   A composition according to claim 6 wherein the micelles or liposomes are capable of transporting the agent through the nasal mucosa to the brain.

9.   A composition according to claim 6 wherein the odorant agent is capable of binding to odorant binding protein.

10.   A composition according to claim 6 wherein the odorant agent is capable of enhancing transport of the neurological agent to olfactory neural receptors.

11.   A composition according to claim 1 further comprising combining the agent with a carrier.

12.   A composition according to claim 1 wherein the agent is transported by means of the olfactory neural pathway into the olfactory bulb, olfactory-connected areas of the brain, the hippocampal formation, amygdaloid nuclei, nucleus basalis of Meynert, locus ceruleus, brainstem raphe nuclei, or any combination thereof.

13.   A composition according to claim 1 wherein the agent is transported to the brain by means of the olfactory system by transneuronal anterograde transport, transneuronal retrograde transport, or any combination thereof.

14.   A composition according to claim 1 wherein the agent is transported to damaged neurons in the brain.

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15.   A composition according to claim 1 wherein the agent is administered to the nasal cavity as a powder, spray, drops, gel, ointment, injection, or infusion.

16.   A composition according to claim 1 wherein the agent is first administered to an eye as drops.

17.   A pharmaceutical composition for use in the diagnosis of brain disorders in a mammal, comprising: a labeled diagnostic neurologic agent in combination with a pharmaceutically-acceptable carrier, wherein the composition is capable of effecting absorption of the labeled neurologic agent into the olfactory neural pathway of the mammal.

18.   A composition according to claim 17 wherein the diagnostic neurologic agent is capable of detecting substructures or biochemical markers associated with a neurologic or psychiatric illness.

19.   A composition according to claim 17 wherein the neurologic agent is a monoclonal antibody, polyclonal antibody, or chemical reagent.

20.   A composition according to claim 19 wherein the antibody is selectively reactive with glycolipid, sulfolipid, phospholipid, or phosphoprotein antigens.

21.   ·   A composition according to claim 19 wherein the antibody is selectively reactive with sulfatide.

22.   A composition according to claim 19 wherein the antibody is labeled by means of a reaction with a second labeled antibody.

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23.   A composition according to claim 17 wherein the labeling agent is radioactive, enzymatic, fluorescent, or any combination thereof.

24.   A composition according to claim 17, further comprising an appropriate amount of lipophilic micelles or liposomes, odorant agent, or any combination thereof.   .

25.   A composition according to claim 24 wherein the agent is contained within the micelles or liposomes.

26.   A composition according to claim 24 wherein the micelles or liposomes are capable of transporting the labeled neurologic agent through the nasal mucosa to the brain.

27.   A composition according to claim 24 wherein the liposomes or micelles are composed of gangliosides, phospholipids, bile salts, detergent-like adjuvants, or any combination thereof.

28.   A composition according to claim 24 wherein the odorant agent is capable of binding to odorant binding protein.

29.   A composition according to claim 24 wherein the odorant agent is capable of enhancing transport of the neurologic agent to olfactory neural receptors.

INTERNATIONAL SEARCH REPORT

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]:   A 61 K 9/08, A 61 K 9/72

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [*]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0145209 (FIDIA SPA) 19 June 1985 see page 1, lines 5-12; page 3, line 26 - page 4, line 18; page 8, line 23 - page 9, line 6; page 9, line 30 - page 10, line 32; page 11, example 2; page 13, lines 11-20; claims 1,16	1,2,4,5,11, 15,16
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X	Proceedings of the National Academy of Sciences, volume 79, July 1982, Medical Sciences, Plc., T.C. Anand Kumar et al.: "Pharmacokinetics of progesterone after its administration to ovariectomized rhesus monkeys by injection, infusion, or nasal spraying", pages 4185-4189 see the whole document, in particular 4188	1,2,5,11-16

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the International filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
3rd April 1991	1 7. 05. 91
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	F.W. HECK

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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X	Yie W. Chien et al.: "Nasal systemic drug delivery", 1989, Marcel Dekker, Inc., (New York, US), see pages 18,19, paragraph 1.9; pages 45-48, paragraph 3.3; pages 55-61, table 3.7; pages 82-84; page 293, paragraph 6.4	1-3,5,11-18
Y		9,10,19-23, 28,29

P,X	EP, A, 0351808 (G.D. SEARLE & CO.) 24 January 1990 see page 2, lines 4-6; page 4, lines 25-27,39-43; page 5, line 53 - page 6, line 20; page 7, formulations F,I; claims 1,8,14,18,21-23	1,2,4-8,17, 18,23-27

X	WO, A, 8604233 (RIKER LABORATORIES, INC.) 31 July 1986 see page 1, lines 5-9; page 3, lines 1-18; page 4, line 31 - page 5, line 19; page 14,15, example 13; claims 1,2	1,2,5-8

Y	FR, A, 2260329 (FAVIERE R.E.) 5 September 1975 see the whole document	9,10,28,29
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Y	WO, A, 8901343 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 23 February 1989 see page 1, lines 5-10,20-24; page 6, line 30 - page 7, line 19; claims 1,2, 4,9	19-23

P,X	Journal of the American Pharmaceutical Sciences, volume 79, no.9, September 1990, American Pharmaceutical Association, Plc., Munir A. Hussain et al.: "Nasal administration of a cognition enhancer provides improved bioavailability but not enhanced brain delivery", pages 771-772 see the whole document, in particular page 772	1,2,4,5,10-16

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The members are as contained in the European Patent Office EDP file on 29/04/91
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